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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/045,375	11/09/2001	John Tallman	99,130-J	5633

7590 12/22/2005

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EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 12/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/045,375	**Applicant(s)** TALLMAN ET AL.	
	Examiner Michael Brannock	**Art Unit** 1649	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 05 October 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☒ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *36-47*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See attachement.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Continuation of 3. NOTE: the limitation "partial angonsit would require further searching and consideration.

Attachment to Advisory Action

Maintained Rejections:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 36-47 rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 6444666 to Ladduwhetty et al. filed 8/27/1998, as set forth previously.

The invention of the instant claims is predicated on the idea that selective activation GABA $\alpha_2 \beta\gamma_2$ or $\alpha_3 \beta\gamma_2$ receptors, while minimizing activation of receptors having $\alpha 1$ subtype, will produce antidepressant effects with minimal sedative and cognitive impairing effects, see pages 33-39.

Patent No: 6444666 teach this principle with regard to anxiety and depression, see the see col 2, lines 10-26, and particularly lines 37-38. *In vivo* confirmation of the response sensitivity, e.g. claims 46 and 47, is also taught, see col 9, lines 1-5. These teaching differs from the instant claims in several insignificant ways. U.S. Patent No: 6444666 does not teach any particular EC_{50}, e.g. that the EC_{50} be less than 200 nM as in the instant claim 37. One of ordinary skill in the art of pharmacology would not need to be taught a particular number to use as this would readily be apparent during routine optimization of operating parameters.

Applicant argues that there is nothing in the cited reference or the prior art as a whole that suggest that an assay for anxiolytic compounds would also identify antidepressants. This

argument has been fully considered but not deemed persuasive. This premise is not the basis of the rejection. Ladduwhetty do not teach that any assay for anxiolytics would identify antidepressants, they teach that particular assays that rely on selective activation GABA $\alpha_2 \beta\gamma_2$ or $\alpha_3 \beta\gamma_2$ receptors, while minimizing activation of receptors having $\alpha 1$ subtype, will identify anxiolytics and antidepressants.

Applicant argues that Ladduwhetty does not teach this selectivity in the context of depression. This argument has been fully considered but not deemed persuasive. One of ordinary skill in the art appreciates that Ladduwhetty teaches the principle at col 2 lines 10-26 and then immediately provides examples, including depression, at lines 37-38. Furthermore, Ladduwhetty distinctly state "such disorders include anxiety disorders,..., and depressive or bipolar disorder..", see lines 30-36 of col 2.

Additionally, Applicant argues that the definition of the compounds referred to, e.g. at lines 37 and 38, is given later at col 3 lines 3-18 and encompasses compounds that are not selective. Applicant uses this argument as the basis for showing that 1) depression is not presented in the context of of anxiety and 2) that Ladduwhetty appear to suggest that something other than selective activation of these subunits accounts for antidepressant activity. This argument has been fully considered but not deemed persuasive. Applicant's interpretation of these teachings is unduly narrow and selective. As discussed above, one of ordinary skill in the art appreciates that Ladduwhetty teaches the principle of selective activation $\alpha_2 \beta\gamma_2$ and $\alpha_3 \beta\gamma_2$ subunits at col 2 lines 10-26 and then immediately provides examples where it is relevant, including depression, at lines 37-38 which, given even the most narrow possible reading of these teachings, would at least suggest to one of ordinary skill in the art that this principle applies to

depression as well as anxiety. Furthermore, that the definition of "compounds of the invention" provided for in a separate section of the description includes compounds that do not display such specificity in no way contradicts the suggestion provided by col 2 that selective activation $\alpha_2\ \beta\gamma_2$ and $\alpha_3\ \beta\gamma_2$ subunits while minimizing alpha-1 subunit activation identifies antidepressants as well as anxiolytics with minimal sedative effects.

Applicant argues that the necessary connection between anxiolytic and antidepressants is simply not in the art. This argument has been fully considered but not deemed persuasive. As admitted by Applicant at page 10, last paragraph, the art recognizes overlap in the treatment of anxiety and depression, although it is agreed that the two disorders are distinct. Thus, one of ordinary skill in the art would view the teachings of Ladduwhetty as describing a molecular underpinning of this overlap, i.e. that $\alpha_2\ \beta\gamma_2$ and $\alpha_3\beta\gamma_2$ are involved in both anxiety and depression.

Applicant argues that U.S. Patent 6444666 (Ladduwahetty) teach only binding assays not functional assays as required by the claims; and that the instant specification teaches that binding assays wrongly identify antagonists as well as the required agonists. This argument has been fully considered but not deemed persuasive as it is premised on an unreasonably poor view of the level of skill of one of ordinary skill in the art of receptor pharmacology, which is quite high. First, Ladduwahetty specifically state that at col 2, line 65: "Desirably, the compounds of the invention will exhibit functional selectivity in terms of a selective efficacy for the alpha-2 and/or alpha-3 subunit relative to alpha-1 subunit. One of ordinary skill in the art would fully and immediately appreciate that this statement directly refers to and encompasses the functional assays referred to by Applicant and widely known and practiced in the art.

Applicant points to the Paul Whiting article as providing evidence that the skilled artisan would only know to conduct conventional screening assays based on binding affinity upon reading the Ladduwahetty patent. This argument has been fully considered but not deemed persuasive Whiting is providing a general review of the art of GABAA receptor study and, in the statement referred to by Applicant, Whiting is actually contrasting the study of GABAA receptors with traditional methods of studying receptors in general. That is, summing-up what is known in the art, Whiting indicates that functional studies of GABAA receptors are most important, see col 1 of page 652. Whiting reviews the art of functional assays of GABAA receptors and points to two references [13,14] (page 648) that were published a decade before Ladduwahetty filed for their patent. Thus, the desirability and routine nature of functional assays of GABAA receptors was old and well established in the art at the time Ladduwahetty patent was filed. As this was well appreciated by Ladduwahetty, the patent states the desirability of functional assays but does not go into great detail as these are well known in the art. In fact, contrary to Applicant's assertion, and apparently escaping the examiner's notice as well, functional assays involving cloned and transfected host cells are taught by Ladduwahetty at col 8 Lines 46-63 and *in vivo* animal assays are taught beginning at line 64.

Conclusion

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649.Please note the new central fax number for official correspondence below:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-

0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867. Official papers filed by fax should be directed to **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

December 19, 2005

ELIZABETH KEMMERER
PRIMARY EXAMINER